FOR ARGUMENT

IN THE

Supreme Court of the United States

October Term, 1978

No. 78-605

THE UNITED STATES OF AMERICA, *et al.*,

Petitioners,

v.

GLEN L. RUTHERFORD, *et al.*,

Respondents.

BRIEF OF AMICUS CURIAE THE COMMITTEE FOR FREEDOM OF CHOICE IN CANCER THERAPY IN SUPPORT OF RESPONDENTS

BRIEF OF RESPONDENT IN OPPOSITION

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INTEREST OF AMICUS CURIAE

The Committee for Freedom of Choice in Cancer Therapy is a California Non-Profit Corporation, with State Chapters in each of the Fifty States.

The Committee for Freedom of Choice in Cancer Therapy was formed and operates to, among other things, encourage, foster and conduct programs for the continuing education and training physicians, nurses, technicians, and others as to all matters concerned with the detection, diagnosis, treatment and prevention of cancer, with particular emphasis on metabolic therapy;

to encourage, foster and conduct programs for the continuing education of the public concerning cancer; to further the proper use of metabolic therapy for the treatment and prevention of cancer; to encourage the provision of adequate facilities wherein metabolic cure and treatment may be accorded to cancer patients; and to otherwise encourage, foster and assist the establishment of programs of service to cancer patients.

The Committee for Freedom of Choice in Cancer Therapy receives contributions, legacies and bequests, and proceeds from fund raising events. The Committee for Freedom of Choice in Cancer Therapy uses these receipts for public education, professional education and cancer research. The Committee for Freedom of Choice in Cancer Therapy is actively concerned with the sponsorship of programs which will encourage research into the causes, treatment, cure and control of cancer; programs of public and professional education; and providing information and assistance to cancer victims.

The Committee for Freedom of Choice in Cancer Therapy has consistently gathered evidence and information demonstrating the efficacy of Laetrile when used in conjunction with a total metabolic program. The activities of the Committee for Freedom of Choice have resulted in a widespread recognition of Laetrile, when included as a component and metabolic therapy, as an effective modality in the treatment alleviation and cure of cancer.

The failure of conventional medical therapies to reduce mortality rate resulting from cancer by use of recommended drugs, radiation, and surgery during the past 45 years demonstrates the need for continuing research for a solution to the problem; and specifically, for the need for further liberalization of laws which restrict such research.

ARGUMENT

1. Whether the safety and effectiveness requirements of the Federal Food, Drug and Cosmetic Act, as applied by the Federal Food and Drug Administration, accomplishes their intended purpose.
2. Whether the constitutional right of privacy protects access to a drug such as laetrile.

I

THE SAFETY AND EFFECTIVENESS REQUIREMENTS OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT AS APPLIED BY THE FEDERAL FOOD AND DRUG ADMINISTRATION FAIL TO ACCOMPLISH THEIR INTENDED PURPOSE.

The Federal Food, Drug and Cosmetic Act, and amendments thereto, were enacted pursuant to the Government's police power to regulate the drug industry because it was felt that the public was largely beyond self-protection from drugs that might be hazardous or ineffective. *United States v. Dotterweich* (1943), 320 U.S. 277, 280; *Weinberger v. Hynson, Westcott and Dunning, Inc.* (1973), 412 U.S. 609, 617-618.

To justify the use of the police power on behalf of the public it must appear, first, that the interests of the public require such regulation and, second, that the means used are reasonably necessary to the accomplishment of the purpose. *Goldblatt v. Hempstead* (1962) 369 U.S. 590, 594-595.

1. While it is conceded that there is a genuine public need to protect the public in general from drugs that are hazardous or ineffective, or both, a close examination of the *manner of implementation* of the Federal Food, Drug and Cosmetics Act by the Federal Food and Drug Administration reveals that the means used are not effectively accomplishing the purpose of the Act in general, and specifically with reference to the disease cancer. As empowered by statute,[1] the Commissioner of the FDA has promulgated regulations[2] governing New Drug Applications. As the years passed, the impact of these regulations grew:

> "There was a steady stream of NDA's under that Act supported by voluminous data. Many new drugs claiming 'me-too' status were marketed illegally or were launched with an advisory opinion of the FDA that they were recognized as safe. It is estimated that by 1969 there were five identical or similar drugs for every drug with an effective NDA. Enormous administrative problems were created. Each NDA contained about 30 volumes, a stack 10 to 12 feet high; and some contained as many as 400 volumes of data." *Weinberger v. Hynson, Westcott & Dunning, supra*, 412 U.S. at page 621.)

The Secretary of Health, Education and Welfare's

[1]21 United States Code, section 371

[2]21 CFR sections 130 et seq.

Task Force on Prescription Drugs found:

> "The various phases of IND and NDA may require several years, 5 years to complete all the requirements is not considered unusual." (*The Drug Prescribers*, Washington, D.C., U.S. Government Printing Office, 1968, page 119.)

The burdens imposed by the 1962 efficacy requirement have also increased:

> "The impact of these requirements on a drug maker was considerable. For example, a Parke-Davis official reported that when the company first marketed a particular epinephrine preparation in 1938, all it had to submit was a 27 page report concerned primarily with safety. In 1948, when it introduced a new expectorant, only a 73 page report was required. Another new drug marketed in 1958 needed a 130 page submission. But in 1962, when Parke-Davis requested FDA approval of its contraceptive Norlestrin, it had to present a report amounting to 12,370 pages. And in 1968, when approval was requested for its new anesthetic Ketamine, the required documents totaled slightly more than 72,000 pages in 167 volumes." (Joseph F. Sadusk, Jr., "The impact of Drug Legislation on Clinical Evaluation of Drugs," paper presented at symposium, Gottlieb Duttweiler Institute, Ruschlikon-Zurich, August 28-29, 1969.)

In October, 1973 Reader's Digest drew the problem to public attention (Walter S. Ross, "The Medicine We Need but Cannot Have," Reader's Digest, October 1973):

> "Since 1963, not a single new general-purpose medicine has been introduced in the United States to treat hypertension, even though twenty-three million Americans are affected by the disease. Yet between 1967 and 1971 five such drugs came into general European practice.
>
> "In the same period, ten medications to treat irregular heartbeat came into the market in Europe, yet by mid-1973 only one of these had been approved for U.S. usage.

"At least seven new medications for asthma were introduced in Europe in 1962. By mid-1973 only two could be prescribed in the U.S.A.

"A study conducted by the University of Rochester's Dr. William Wardell found that of the eighty-three new medicines adopted in both Britain and the U.S. between 1962 and 1971, more than half were introduced first in Britain — and an average of 2.8 years elapsed before the FDA allowed them to be sold in this country."

The practical effects of Section 505 (21 U.S.C. section 355) as implemented by the FDA are being felt by the United States citizen:

"Indeed, it is altogether possible that Americans could become a "have not" people in their access to medication with the fruits of chemical and technological improvement created here exported to others but denied us. *Medical Economics* observes that three-quarters of the new drugs being developed by American pharmaceutical firms are going exclusively to people in other lands and are barred from use in America.

"In a similar vein, seven new asthma medications have been introduced in Europe in the past decade, but only two of these have made it to the United States. Forty-seven new medications to treat heart and circulatory problems came on the world market between 1967 and 1971, but only six were made available in this country. Five new drugs for the treatment of hypertension have recently appeared in Europe, but no new general-purpose hypertension medicine emerged in America between 1963 and 1972.

"It is noteworthy that penicillin, if discovered today, probably could not pass the relevant tests of the bureaucracy. After all, the drug does cause unfavorable reactions in some people, and it is less effective in certain cases than in others — considerations that could flunk it on FDA's "safe and effective" meter. Yet penicillin has saved thousands of people from pain and death, and only a fanatic or perhaps a bureaucrat would contend that humanity would be better off without it."[3]

"Regulatory tightness in the U.S.A. has been such that important pharmaceuticals have been available in other countries and not in America. Importation and use without FDA clearance is not permitted and so the armory of drugs available to the American physician has suffered a relative decline. The contrast in availability has been most marked in cardiovascular, diuretic, respiratory and gastrionentinal areas compared with Britain. In wider and numerical terms '. . . up to the end of 1971 the overall British lead for mutually available drugs was, in terms of drug-years of prior availability, double that of the United States. In terms of exclusively available drugs, Britain has nearly four times as many as the United States.' "[4]

The cost of bringing a new drug through the bureaucratic maze to NDA approval has risen from an average of $1.3 million in 1969 to $10.5 million in 1970,[5] and to $24.4 million in 1973.[6]

Since there has been an increasing cost factor in the production of new drugs, the "cost-benefit ratio" becomes exceedingly important to the drug companies. At some point in the NDA process, the drug manufacturer will *patent* the drug so that it may reap the benefits of the research it has incurred and pass these costs on to the consumer and drug company licensees. Since other drug

[3]M. Stanton Evans, "Government Can Be Hazardous to Your Health," Imprimis, Vol. 4 No. 6, June 1975

[4]J. E. S. Parker, Regulating Pharmaceutical Innovation: An Economist's View, 32 Food, Drug, Cosmetic L.J. 160, 172

[5](H. A. Clymer, "The Changing Costs and Risks of Pharmaceutical Innovation," and V. A. Mund, "The Return on Investment of the Innovative Pharmaceutical Firm," both in *The Economics of Drug Innovation*, ed. J. D.Cooper, Washington, D.C., The American University, 1970).

[6](National Science Foundation, *A Price Index for the Deflation of Academic R & D Expenditures*, page 2)

companies can use "me-too" copies of an NDA drug (*USV Pharmaceutical Corp. v. Weinberger* (1973), 412 U.S. 655), the patent is of crucial importance in recovering research costs and costs of obtaining the NDA. The concern for profit also makes it clear that it is not profitable to obtain a NDA on a substance, such as laetrile, which is in the common domain as a common chemical and cannot be protected by patent.

An example of this problem is found in *United States v. Evers* (M.D. Ala., 1978), 453 F. Supp 1141. In *Evers, supra*, the drug EDTA (Calcium disodium versenate) was approved by the FDA for chelation treatment of heavy metals poisoning. Dr. Evers was charged with mislabeling of EDTA because he was using it to treat patients for arteriosclerosis, a purpose for which there was no NDA approval. (*U.S. v. Evers, supra*, page 1147.) The District Court observed (at page 1149-1150):

> ". . . New uses for drugs are often discovered, reported in medical journals and at medical meetings, and subsequently may be widely used by the medical profession. But the Federal Drug Administration does not permit the package insert to be amended to include such uses *unless the manufacturer submits convincing evidence supporting the change. The manufacturer may not have sufficient commercial interests or financial wherewithal to warrant following the necessary procedures to obtain FDA approval for the additional use of the drug. . . .*" (Emphasis added.)

The court in *Evers, supra*, was caught between the Scylla of recognizing that neither a private citizen, the patient nor the physician could afford to undertake the NDA process, and the Charybdis of recognizing the need to protect the public from unsafe and or inefficient

drugs. Indeed, *Rutherford v. American Medical Association* (CA 7, 1967), 379 F. 2d 641, 643, cert. denied 389 U.S. 1043, the Court of Appeals held that the plaintiffs cancer victims were held to be required to make "an attempted good faith application for application for approval or exemption" for an NDA before their claim could be heard. The Court of Appeals observed (379 F. 2d at page 643):

> ". . . The fact that compliance might be expensive and burdensome is not unfairness in the procedure, but a consequence of a reasonable Congressional scheme for the introduction of new drugs."

While there is "rational justification" for the Federal Food, Drug and Cosmetic Act, amici suggests that compliance has become so expensive and burdensome that there are now "Lines drawn on the basis of wealth . . . (which) . . . are traditionally disfavored" (*Harper v. Virginia Board of Elections* (1966), 383 U.S. 663, 668;), which violates the Equal Protection Clause by discriminating against the average citizen in favor of multimillion dollar drug manufacturers. Cf. *Ortwein v. Schwab* (1973), 410 U.S. 656, 659; *United States v. Kras* (1973), 409 U.S. 434; *Boddie v. Connecticut* (1971), 401 U.S. 371.

The Doctrine of Informed Consent places upon the physician a legal duty to disclose the risks inherent in each of the therapeutic alternatives available to the patient, in order that the patient may make an informed exercise of his choice of a particular course of medical treatment. *Canterbury v. Spence* (CA DC, 1972), 464 F2d 772, 780-782. The Doctrine of Informed Consent in es-

sence gives the patient the right to choose to be a "human guinea pig." It has been suggested that a system of "monitored release" would be a practical solution to the problem, and unproven drugs which pass the test of safety could be granted "conditional acceptance" for use by physicians under a closely monitored system using informed, consenting patients until a sufficient amount of data had been accumulated to establish the drug as effective or ineffective.[7] It would be relatively simple for the FDA to establish protocols for the physician's use in treating the patient and criteria for evaluating the results in terms of efficacy. Such a procedure would reduce the expense of the NDA, would reduce the length of time necessary to complete the NDA procedure, and would give the patient dissatisfied with orthodox treatment an alternative solution to the present dilemma of "orthodox treatment or no treatment."

2. Inherent in the Federal Food, Drug and Cosmetic Act is the premise that, through the statutory scheme enacted, safe and effective drugs will be found for each and every illness. While medicine has made almost miraculous strides in curing many other diseases, such is not the case with cancer. The *6th National Cancer Conference Proceedings*[8] jointly sponsored by the American Cancer Society and the National Cancer Institute (HEW) illustrate the deficiencies of conventional treatment:

At Page 513: *Robert D. Sullivan, M.D.*, Department of Cancer Research, Lahey Clinic Foundation, Boston:

> "There has been an enormous undertaking of cancer research to develop anticancer drugs for use in the management of neoplastic diseases in man. However, progress has been slow, and no chemical agents capable of inducing a general curative effect on disseminated forms of cancer have yet been developed."

At Page 33: *William Powers, M.D.*, director, Division of Radiation Therapy, Washington University School of Medicine, St. Louis:

> "Although preoperative and postoperative radiation therapy have been used extensively and for decades, it is still not possible to prove an unequivocal clinical benefit from this combined treatment . . . Even if the rate of cure does improve with a combination of radiation and therapy, it is necessary to establish the cost in increased morbidity which may occur in patients with or without favorable response to the additional therapy."

At Page 609: *James F. Holland, M.D.*, Rosewell Park Memorial Institute, New York State Department of Health, Buffalo, N.Y.:

> "Human cancer are refractory in large part to cure by the chemotherapeutic approaches which have been tried . . ."

At Page 855: *Philip Rubin, M.D.*, Chief, Division of Radiotherapy, University of Rochester Medical School, Strong Memorial Hospital, Rochester, N.Y.:

> "With thousands of lung cancer patients treated by irradiation, the value of radiation therapy should be clearly established or disestablished. The indictment of Radiotherapy in the treatment of this disease by Kraut ('The Question of Irradiation Therapy in Lung Cancer,') JAMA 195 (1966: 177-81) is a carefully researched document that has to be considered. The clinical evidence and statistical data in numerous reviews are cited to illustrate that no increase in survival has been achieved by the addition of irradiation."

[7] *People v. Privitera: The Right to Prescribe and Use Laetrile* (1978), 5 Western State University Law Review, 201, 227-229.

[8] Lippincott, 1970

At Page 163: *Vera Peters, M.D.*, Princess Margaret Hospital, Toronto, Ont."

> "Shimkin (*'End Results in Cancer of the Breast,'* Cancer 20 (1967): 1039-13) has shown recently that in carcinoma of the breast, the mortality rate still parallels the incidence rate, thus proving that there has been no true improvement in the successful treatment of the disease over the past thirty years, even though there has been technical improvement in both surgery and radiotherapy during that time."

At Page 153: *Robert L. Egan, M.D.*, Professor of Radiology and Chief, Mammography Section, Emory University School of Medicine, Atlanta, Ga.; and R. Waldo Powell, M.D., Associate Professor of Surgery, Department of Surgery:

> "The thirty-year monotonous plateau of the death rate for breast cancer has persisted despite physicians' awareness of breast cancer, refinement of methods of inspecting and palpitating the breast, educating women in self-examinatio, improvements in radiotherapy that include supervoltage, use of more extensive surgical procedures, and the use of chemotherapy and hormones."

At Page 421: I.H. Gillespie, M.D.; H. T. Debas, M.D. and F. Kennedy, University Department of Surgery, Western Infirmary, Glasgow, Scotland:

> "Since there is yet no sign that either radiotherapy or chemotherapy can offer real therapeutic benefit to patients with gastric cancer, the main hope at present for either cure, or useful palliation, rests with surgical treatment. The many varied surgical approaches do not seem to have made a great difference to the overall outcome in large series of patients, and it seems unlikely that much improvement can be expected from further developments of surgical technique."

At Page 83: *Saul A. Rosenberg, M.D.*, associate professor of Medicine and Radiology, Stanford University School of Medicine, Palo Alto, California:

> "Thus, worthwhile palliation is achieved in many patients however, there still will be the inevitable relapse of the malignant lymphoma, and, either because of drug resistance or drug intolerance, the disease will recur, requiring modifications of the chemotherapy program and eventually failure to control the disease process. With very few exceptions, cure is not achieved despite the dramatic initial benefit which is seen in so many patients."

At Page 379: *John D. Trelford, M.D.*, F.R.C.S., Department of Obstetrics and Gynecology, Ohio State University Hospital:

> "At the present time chemotherapy of gynecological tumors does not appear to have increased life expectancy except in sporadic cases . . . There appears to be no satisfactory method of determining to which drug a tumor will be sensitive. The only basis of selecting a drug is by past experience. The problem of blind chemotherapy means not only a loss of the effect of the drugs, but also a lowering of the patient's resistance to the cancer cells owing to the toxicity of these agents . . . At the present time there is no satisfactory method of stimulating or mobilizing the host's immunological defenses to aid in controlling or eradicating the patient's malignancy."

Dr. Hardin Jones of the University of California at Berkeley indicated that, with the exception of child leukemia and possibly Hodgkin's disease, there has been no reduction in the incidence of deaths from cancer in the United States and the western world since 1911, despite the best efforts of medical science; and that cancer victims receiving no medical treatment live longer than victims receiving treatment ". . . and for some of the common kinds of cancers, such as breast cancer, this amounts to a considerable factor, approximately a factor of four (time longer)." (R 507, pp. 4634-4635, 4656-4659)

Counsel for Petitioner acknowledges the severity of

the problem (Petitioner's Opening Brief, fn. 21) by pointing out that the FDA has over 300 oncologic drugs under clinical investigation, and that the NCI screens from 15,000 to 30,000 potential anti-cancer drugs each year.

The ineffectiveness of contemporary cancer treatments coupled with the intensive research to find a cure and the invidious resistance of cancer to cure, strongly emphasizes that at present the standard of "efficacy" applied to cancer by the FDA must be extremely low. This in turn casts doubt upon the existence of a "rational basis" of the "efficacy requirement" as it applies to cancer drugs in general, and laetrile in particular. (*Weinberger v. Hynson, Westcott & Dunning, Inc., supra*) That *United States v. Rutherford*, the present case before this court, was certified as a class action by the trial judge (WD Okla, 1977; 429 FSupp 506) gives strong indication that a great number of people are seeking metabolic treatment which includes administration of laetrile because *there are no* "effective" cancer drugs or treatments, and because they feel that metabolic therapy which includes laetrile is a safer and more preferable alternative to chemotherapy, radiation and surgical treatment.[9] Likewise, the enormous magnitude of the problem created by the FDA's implementation of the NDA policy to laetrile and other non-profitable cancer drugs, and the cancer victim's rejection of orthodoxy's failures, is indicated by

[9]The United States Department of Health, Education and Welfare's National Institute for Occupational Safety and Health has published the *Registry of Toxic Effects of Chemical Substances* (1976), which was written with the objective "to identify all known toxic substances." Laetrile (amygdalin) is not listed therein, apparently because it is not considered toxic; however, toxicity figures are readily available. (Manner, H. W.; *The non-toxicity of Amygdalin to laboratory mice*, Sci. Biol. J., p. 347-349 (May-June 1977).) A comparison of Laetrile toxicity with the toxicity of other common drugs in terms of milligrams per kilogram of body weight:

Test Animal	Laetrile (Amygdalin)	Amphetamine	Aspirin	Digitalis
Mouse, oral	150 mg kg	15 mg kg	815 mg kg	3.5 mg kg
Mouse, intraperitoneal	9500 mg kg	23 mg kg	195 mg kg	5.5 mg kg
Mouse, intravenously	9400 mg kg	18 mg kg	681 mg kg	20 mg kg

Tetracycline	Cytoxan[a]	Actinomycin D[a]	Vitamin B1 (Thiamine)
808 mg kg	91 mg kg	13 mg kg	8221 mg kg
125 mg kg	240 mg kg	.07 mg. kg	220 mg kg
291 mg kg	160 mg kg	.046 mg kg	89 mg kg

It is clear that the lower the figure for the lethal dose, the more toxic the drug is. Conversion to 'Probable Human Lethal Dose' classification applicable to the foregoing drugs is as follows (Casarett, L. J. and J. Doul, *Toxicology*, Macmillan Pub. Co. (1975).):

Toxicity	Commonly Used Term	Probable Human Lethal Dose 70 kg. (150 lb.) man
6	Supertoxic	less than 5 mg kg — less than 7 drops
5	Extremely toxic	5 to 50 mg kg — 7 drops to 1 tsp
4	Very toxic	50 to 500 mg kg — 1 tsp to 1 ounce
3	Moderately toxic	500 mg kg to 5 g kg — 1 oz to 1 pint
2	Slightly toxic	5 to 15 grams kg — 1 pint to 1 quart
1	Practically nontoxic	over 15 grams kg — over 1 quart

As these authorities show, Laetrile is only slightly toxic in injectable form and is safer than all other injectables compared to it; and in oral form is safer than amphetamines, and almost as safe as aspirin.

Counsel for Petitioner United States correctly acknowledges that "No drug is completely "safe" in the lay person's sense of the word, since every drug — aspirin not excepted — involves risks." (Petitioner's Brief, p. 21.)

the large quantities of laetrile brought into this country

illegally[10], the number of governmental civil actions to prevent manufacture and distribution,[11] legal actions brought by cancer victims,[12] the large number of cancer victims making the "Mexican laetrile connection,"[13] and the number of cancer victims within the United States being treated with laetrile.[14]

The issue of the toxicity of laetrile is a phantom issue, in any event, as University of New Mexico School of Law

[10] *United States v. Richardson* (CA 9, 1978) 588 F. 2d 1235, *United States v. Luther* (CA 9, 1975), 521 F. 2d 408; *United States v. Westover* (CA 9, 1975), 511 F. 2d 1154; *United States v. Medina-Carbajal*, Cr. No. 15896 (S.D. CA, 1973); *United States v. De Garrido*, Cr. No. 16053 (S.D. CA, 1973) *United States v. Guillent*, Cr. No. 74-405 (S.D. CA, 1974); *United States v. Bonilla* Cr. No. 75-0732 (S.D. CA, 1975); *United States v. Alvarez-Horta*, Cr No. 75-1026 (S.D. CA, 1975); *United States v. Weisman*, Cr. No. 75-1493 (S.D. CA, 1975); *United States v. Gonzales-Pacheco*, Cr. No. 75-1921 (S.D. CA, 1975); *United States v. Mejia-Mejia*, Cr. No. 76-0050 (S.D. CA, 1975); *United States v. Turner* (CA 2, 1977), 558 F. 2d 46.

[11] *United States v. Articles of Food and Drug*, (E.D. WI, 1978), 449 FSupp 497; *United States v. Spectro Foods Corp.: (CA 3, 1976), 544 F. 2d 1175; United States v. General Research Laboratories* (C.D. CA, 1975), 397 FSupp 197; *United States v. Article of Drug . . . Laetrile (Krebs Laboratories* (D ID, 1965), No. 8507; *United States v. Hawk* (S.D. CA, 1963), Civ. No. 8082; *United States v. Mosinee Research Corp* (CA7, 1978), 583 F. 2d 930; *Hanson v. United States* (D. MN, 1 976), 417 FSupp 30, aff'd 540 F2d 947 (CA8, 1976); *United States v. Earthco* (C.D. CA, 1979), Civ. No. 78-3602; *Gadler v. United States*, (D MN, 1977); 425 FSupp 30.

[12] *Rizzo v. United States* (E.D. NY, 1977), 432 FSupp 356; *Carnohan v. United States* (S.D. CA, 1977), Civ. No. 77-0100; *Mattson v. United States* (N.D. CA, 1977), Civ. No. 77-0300; *Keene v. United States* (S.D. W. Va., 1976), Civ. No. 76-249; *Rutherford v. American Medical Ass'n* (CA 7, 1967), 379 F. 2d 641, cert. denied, 389 U.S. 1043; *Durovic v. Richardson*, (CA 7, 1973), 479 F. 2d 242, cert. denied 414 U.S. 944.

[13] 17,000 per year, according to the *Rochester* (Minn.) *Post-Bulletin*, series of January 21-25, 1974.

[14] *At least* 75,000 cancer victims are currently treating with laetrile. Harper, Harold W., M.D. and Michael L. Culbert *How You Can Beat the Killer Diseases*. Arlington House (1978).

assistant professor Robert L. Schwartz observes:[15]

> ". . . Before laetrile became a political issue, almost all the formal medical research demonstrated, or assumed that laetrile was nontoxic. The only evidence the medical profession has offered to show that it is poisonous appears to be in direct support of the medical profession's political arguments. . . . No study has shown that the dosage recommended by physicians who prescribe laetrile in the United States even approaches the toxic level."

It must also be noted that the very concept and future of metabolic therapy — the use of vitamins, minerals and enzymes to improve the body's over-all health and cancer-fighting capabilities — will be affected by the outcome of this case, since vitamin-mineral-enzyme combinations are not proven "safe and effective" for the treatment of cancer and are therefore mis-branded. *United States v. Evers, supra.* Nobel Prize Laureate Linus Pauling has found evidence that mega-doses of vitamin C are efficacious in treating cancer; Frank Chytell, M.D. and David Ong, M.D. of Vanderbilt University have found evidence that mega-doses of vitamin A are efficacious in treating cancer; and Warren Bollag, M.D. of Hoffman-LaRoche Research Laboratory in Basil, Switzerland has found vitamin A to be efficacious in treating topical cancer tumors, in addition to thousands of other physicians who are currently using vitamins, minerals and enzymes for cancer treatment. Concededly, the use of these innocuous substances for treatment of cancer will cause them to be classified as

[15] 65 American Bar Association Journal, 224, 225 (February 1979).

drugs because of the intended use of the substance. 21 U.S.C. section 321(g)(1)(B); *United States v. "Vitasafe Formula M,"* 226 F. Supp 266, 278 (DNJ 1964), *remanded on other grounds*, 345 F. 2d 864 (CA 3, 1965) *cert. denied*, 382 U.S. 918. Nor is it likely that those with the financial capability of pursuing the NDA process — the major drug companies — will be willing to do so since vitamins, minerals and enzymes are currently in the common domain and, hence, there are no profits to be made nor even the opportunity to recover costs of the NDA process.[16]

Finally, it must be noted that one of the risks involved in the "New Prohibition" imposed against laetrile is that cancer victims who reject orthodox treatment are forced into "self-treatment" which, because of the patient's ignorance of medical matters, can be very hazardous.[17]

Counsel for amicus suggests that, notwithstanding the Court's ruling on the right of privacy issue, this Court should find that the means used by the FDA in its quest for "safety and efficacy" are not reasonably related to the intended objectives.

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[16]It is also clear that the NDA process must be followed for *combinations* of drugs, i.e., the combination must be generally recognized as safe. *United States v. Article of Drug Entrol-C Medicated* (CA 9, 1975), 513 F. 2d 1127.

[17]As pointed out by amici State of California and American Cancer Society briefs in the case of Jo Anne Pye, who may have died of cynanide toxicity and who was treating herself. The autopsy report also reflected fluid in the lungs, and kidney and liver failure. Statements from witnesses reflect that Jo Anne Pye was self administering laetrile rectally. Rectal administration of laetrile is strongly discouraged by physicians because of the high danger involved. See Appendix A17

II

THE CONSTITUTIONAL RIGHT OF PRIVACY PROTECTS ACCESS TO A DRUG SUCH AS LAETRILE.

It is conceded at the outset that the constitutional guarantee of personal privacy (*Palko v. Connecticut* (1937), 302 U.S. 319) is not absolute, and that it is to be balanced against important state interests in regulation (*Roe v. Wade* (1973), 410 U.S. 113, 154). However, *Roe v. Wade* also notes (410 U.S. at 155):

> "Where certain 'fundamental rights' are involved, the Court has held that regulation limiting these rights may be justified only by a 'compelling state interest,' (citations) and that legislative enactments must be narrowly drawn to express only the legitimate state interests at stake. (citations)"

Since it is well established that the purpose of the Federal Food, Drug and Cosmetic Act is to protect the public at large from unsafe and ineffective drugs, the right to privacy must be weighed against this state interest.

An examination of recent state and federal right to privacy cases reveals that there is an *additional* factor which the courts consider — whether the impact of the exercise of the right will affect *only* the individual concerned, or whether it will affect the *public at large*. *Roe v. Wade, supra* (approving abortions for the *class* 'pregnant women desiring,' while affirming the state's right to regulate matters pertaining to the health of members of that class); *Doe v. Bolton* (1973), 410 U.S. 179 (striking state regulations pertaining to abortions for the class 'pregnant women' not rationally related to safety,

while affirming the physician's "independent judgment"); *Griswold v. Connecticut* (1965), 281 U.S. 479 (affirming contraception for the class 'women' under right to privacy, while affirming the state's right to ban unsafe contraceptives); *Eisenstadt v. Baird* (1972), 405 U.S. 438 (no rational basis to outlaw contraceptives for the class 'single women' but not the class 'married women;' violated right of privacy); *Loving v. Virginia* (1967) 388 U.S. 1 (no rational basis for invading right of privacy of 'married people' to prevent interracial marriages); *Whalen v. Roe* (1977), 429 U.S. 589 (right to privacy bowed to state registration of 'Schedule II' drug users because the class of drugs was subject to abuse by the class of 'drug users'); *Planned Parenthood of Missouri v. Danforth* (1976), 428 U.S. 52 (no rational basis to prohibit saline amniocentesis abortion procedure to class, because safe, as against right to privacy); *Carey v. Population Services International* (1977), 431 U.S. 678 (no rational basis to prohibit certain contraceptive devices proven safe to class of 'users' in face of right to privacy); *Fitzgerald v. Porter Memorial Hospital* (CA 7, 1975), 523 F. 2d 716 (Right to privacy bows to health safety precautions in maternity delivery room); *Jacobson v. Massachusetts* (1905), 197 U.S. 1 (right to privacy bows to compulsory smallpox vaccination to protect public at large from health hazard of possible epidemic); *Gray v. State* (Alaska, 1974), 525 P. 2d 521 (right to privacy shields ingestion of food, beverages, other substances, absent a compelling state interest); *People v. Raven* (Alaska, 1975), 537 P. 2d 494 (right to privacy protects possession, ingestion of marijuana to class of users

because no legitimate state interest; right to privacy bows when adolescents or driving under the influence involved because legitimate state interest); *White v. Davis* (Cal., 1975), 13 C. 3d 757 (Right to privacy protects college classroom, class 'students,' from governmental spying); *Burrows v. Superior Court* (Cal., 1974), 13 C. 3d 238 (Right to privacy protects bank records unless probable cause and warrant); *Valley Bank of Nevada v. Superior Court* (Cal., 1975), 15 C. 3d 652 (civil discovery shall be weighed against right to privacy prior to disclosure of bank records); *Britt v. Superior Court* (Cal., 1978), 20 C. 3d 844 (Right to privacy protects medical records against civil discovery unless shown relevant to the case); *Tavernetti v. Superior Court* (Cal., 1978), 22 C. 3d 187 (Right of privacy protects against citizen eavesdropping on telephone); *Matter of Quinlan* (N.J., 1976), 70 N.D. 10, 355 A. 2d 647 (state interest in preservation of life bows to right of privacy in choice to refuse life-preserving medical treatment); *Estate of Brooks* (Ill., 1965) 32 Ill. 2d 361, 205 N.E. 2d 435 (same); *Superintendent of Belchertown State School v. Saikewicz* (Mass., 1977), 379 N.E. 2d 418 (right to privacy embraces cancer patient's right to refuse chemotherapy to treat Leukemia; state has no interest in intervening in choice of treatment). The Massachussetts Supreme Court observed in *superintendent of Belchertown, supra*, (379 N.E. 2d at 426):

> "The constitutional right to privacy, as we conceive it, is an expression of the sanctity of individual free choice and self-determination as fundamental constituents of life. *The value of life* as so perceived *is lessened* not by a decision to refuse treatment, but *by*

the failure to allow a competent human being the right of choice." (Emphasis added.)

The individual right to choose one's own medical treatment, or to refuse medical treatment altogether, is a choice which does not affect the public at large. While there is a rational basis for the government to wish to protect the public at large from unsafe, ineffective drugs, this 'compelling state interest' diminishes considerably and the right to privacy is correspondingly strengthened in two situations: (1) where the patient makes a personal choice to select one cancer treatment in preference to another, or declines treatment; and (2) where the patient chooses to become a 'human guinea pig' after being fully advised of the risks inherent in each of the accepted therapeutic alternatives, and of the experimental treatment.[18] The seriousness of the impact of cancer on society and the individual,[19] and the shortcomings of present treatments readily explains the "political revolt against what many people find to be unwarranted

[18]Over 300 oncological drugs are under clinical investigation, and 97,800 individual cancer victims were 'human guinea pigs' in 1977. Brief for the United States, fn. 21. Presumably, these drugs had shown promise and had been determined to be 'safe' at certain dosages, and are being tested on humans to establish whether or not they are effective.

[19]"*1977 Cancer Facts and Figures* by the American Cancer Society estimates that 1977 will have produced an estimated 690,000 new cancer cases; and that over 54 million Americans now living will eventually have cancer, which is one out of every four Americans living. The pamphlet also states that over the years cancer will strike in approximately two of every three families, that in the 1970's there will be an estimated 3.5 million cancer deaths, 6.5 million new cancer cases, and more than 10 million people under medical care for cancer. Only about 1/3 of all people who get cancer this year will be alive five years after treatment, according to the publication." *Rutherford v. United States* (WD OK, 1975), 438 FSupp 1287, fn. 27.

government intervention in their private lives."[20]

There is a relatively small class within the much larger class 'cancer patients' who wish to include laetrile in their treatment. They are willing to be the informed, consenting 'guinea pigs' necessary to prove or disprove the efficacy of laetrile. They are geographically distributed throughout the United States, and are not able to participate in a centrally located program such as the National Cancer Institute might offer, yet they do wish for medical care and supervision while pursuing their chosen course of unorthodox therapy, as a preference to self-treatment. Many have returned from the laetrile clinics in Mexico, only to find that physicians are reluctant to take them as patients because of the illegality associated with laetrile and the risk to their medical licenses. Some of these cancer victims have been 'written off' by orthodoxy, and all wish to improve the quality of their lives. The wide anti-laetrile publicity generated by the American Cancer Society, the American Medical Association, the Federal Food and Drug Administration, and other political opponents of laetrile, has put them on notice that most medical authorities regard laetrile as worthless, a sham, a fraud, so that they are aware of the risks undertaken by becoming a 'human guinea pig.' *The risk of knowingly choosing to become a 'human guinea pig' does not affect the public at large; it affects only the individual making the choice to take the risk.* Just as the right to privacy protects the individual's right to refuse treatment (*Superintendent of Belchertown,*

[20]Schwartz, *Laetrile: The Battle Moves into the Courtroom*, 65 American Bar Association Journal, 224, 226 (February, 1979)

supra; Matter of Quinlan, supra), the right of privacy should protect the individual's right to intelligently choose an unorthodox medical treatment, notwithstanding the recent California Supreme Court decision in *People v. Privitera* (Cal., 3-15-79), ___ C. 3d ___.[21] to the contrary.

The error that the California Supreme Court has made in *People v. Privitera, supra*, is to interpret *Whalen v. Roe, supra* to mean that (1) the state may totally prohibit *all* drugs within a certain class; and (2) that the right to privacy does not include medical treatment. The California Supreme Court stated (slip opinion, p. 5):

> "However, a fundamental privacy right is not at stake here. The interest defendants allege is, apparently 'the interest in independence in making certain kinds of

[21]In an incredibly shallow opinion, the California Supreme Court upheld a conviction obtained under the "anti-cancer quackery" statute enacted by the California legislature in 1959. The legislative findings (California Health & Safety Code section 1700) indicate an intent to protect against *"misrepresentations . . . misleading to the public"* because "It has established that the accurate and early diagnosis of many forms of cancer, followed by prompt application of methods of treatment which are scientifically proven, either materially reduces the likelihood of death from cancer or may (sic) materially prolong the useful life of individuals suffering therefrom."

Follwing the "rational basis test," the California Supreme Court found "a fundamental privacy right is not at stake here," that the 'important decisions' recognized by the United States Supreme Court ". . . do not include medical treatment," and that a rational basis existed for the statute. Dissenting Justice Newman detected no compelling need to abridge the right to privacy; and dissenting Justice Bird adopted in full the extremely lucid, well written opinion of Justice Staniforth in the lower court.

Thus has California abandoned the mainstream of opinion set by other state supreme courts (*Matter of Quinlan, supra; Superintendent of Belchertown, supra; Gray v. State, supra*), leaving matters in the hands of the legislature, where a bill is being introduced to legalize laetrile, as has now been done in 19 other states.

> important decisions.' (Whalen v. Roe (1977) 429 U.S. 589, 599-600.) But the kinds of 'important decisions' recognized by the high court to date as falling within the right to privacy involve 'matters relating to marriage, procreation, contraception, family relationships, and child rearing and education.' (Whalen v. Roe, *supra*, 429 U.S. at p. 600, fn. 26 quoting Paul v. Davis (1976) 424 U.S. 693, 713), *but do not include medical treatment.*
>
> "For this reason defendants' reliance on Roe v. Wade, *supra*, 410 U.S. 113, is misplaced. . . ."

Whalen v. Roe, supra, dealt with the state's right to require registration and regulation of dangerous drug prescriptions (opium and derivatives, cocaine, methadone, amphetamines and methaqualone), while recognizing that a state could *not* ban *all* drugs within a class that had medical usage, and that there was, indeed, a right to privacy included in medical treatment. The Court observed (429 U.S. 603):

> ". . . Clearly, therefore, *the statute did not deprive the public of access to these drugs.*
>
> "Nor can it be said that any individual has been deprived of the right to decide independently, with the advice of his physician, to acquire and to use needed medication. Although the State no doubt could prohibit entirely the use of *particular* Schedule II drugs, it has not done so. This case is therefore unlike those in which the Court held that a total prohibition of certain conduct was an impermissible deprivation of liberty. Nor does the State require access to these drugs to be conditioned on the consent of any State official or other third party. Within dosage limits which appellees do not challenge, *the decision* to prescribe, or to use, *is left entirely to the physician and patient.*"

What the California Supreme Court has done is upheld a ban on *all* experimental drugs unless *proven*

safe *and effective*,[22] thus limiting California cancer victims to the choice of "orthodox treatment" or declining treatment altogether, denying them access to experimental programs, whether government sponsored or otherwise. Such law clearly violates the spirit and letter of *Whalen v. Roe*, *supra*, *Roe v. Wade*, *supra*, and other cases affirming the right to privacy relating to medical care.

[22]California Health & Safety Code section 1707.1 provides:

"The sale, offering for sale, holding for sale, delivering, giving away, prescribing or administering of any drug, medicine, compound or device to be used in the diagnosis, treatment, alleviation or cure of cancer is unlawful and prohibited unless (1) an application with respect thereto has been approved under Section 505 of the Federal Food, Drug and Cosmetic Act (21 USC Section 355), or (2) there has been approved an application filed with the board setting forth:

(a) Full reports of investigations which have been made to show whether or not such drug, medicine, compound or device is safe for such use, and whether such drug, medicine, compound or device is effective in such use;

(b) A full list of the articles used as components of such drug, medicine, compound or device;

(c) A full statement of the composition of such drug, medicine, compound or device;

(d) A full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug, medicine, or compound or in the case of a device, a full statement of its composition, properties and construction and the principle or principles of its operation;

(e) Such samples of such drug, medicine, compound or device and of the articles used as components of the drug, medicine, compound or device as the board may require;

(f) Specimens of the labeling and advertising proposed to be used for such drug, medication, compound or device."

CONCLUSION

It is respectfully submitted that the judgment of the court of appeals should be affirmed on the grounds relied on by the district court. *United States v. New York Telephone Co.* (1977), 434 U.S. 159, 166 n. 8.

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APPENDIX

THE FOCAL ACTION OF AMYGDALIN IN THE METABOLIC THERAPY OF CANCER

By Robert W. Bradford and Henry W. Allen

In any discussion of amygdalin and its metabolism it becomes necessary as a first step to distinguish between the terms "amygdalin" and "laetrile." Fortunately, a great effort has recently been made to clarify these words.

Drug containers presently used in cancer therapy which bear the label "Laetrile" contain no laetrile but only amygdalin. Laetrile, as properly — if not commonly —defined, is not at present commercially available.

Amygdalin is a specific natural substance which may be isolated from various sources, notably apricot and peach kernels, cherry stones, bitter almonds and other seeds of the genus Prunus. Chemically, it is D-l-mandelonitrile gentiobioside, or D-mandelonitrile coupled to the disaccharide, gentiobiose, formed from two molecules of D-glucose.[1] The naturally occurring cyanohydrins of this

type are known as cyanogenic glycosides.[52] The empirical formula for amygdalin is $C_{20}H_{27}NO_{11}$.

In contrast, laetrile is D-l-mandelonitrile glucuronide formed from the same aglycon but with the disaccharide replaced by glucuronic acid. The term "laetrile" is frequently used by laymen to designate all cyanogenic glycosides. The term "laetrile" is generally used by chemists to designate a specific biosynthesized molecule from the degradation product of amygdalin having the empirical formula $C_{14}H_{15}NO_7$.

BIOCHEMICAL PATHWAYS (Introduction)

The biochemical pathway of amygdalin will be briefly described. The first reaction is the cleavage of the exposed glucose at the oxygen linkage to the inner sugar. This is accomplished by the enzyme Beta-glucosidase found in various tissues[53] and bound to the inside of the lysosomal membrane.[54] One molecule of glucose is split off leaving the residue known as prunasin. The action is repeated with the liberation of the second glucose and the formation

of D-d-mandelonitrile.[2] This compound also contains a secondary alcohol group, which leads to some intriguing biochemical considerations concerning the detoxification process in humans of alcohols and amines, which is discussed later.

STEREOCHEMISTRY OF AMYGDALIN

The scientific designation for amygdalin, D-l-mandelonitrile beta-diglucoside describes the compound's configuration, optical activity and composition.

The capital "D" designates the absolute configuration in a configurational sense only. The lower case "l" denotes the direction that polarized light rotates when passed through the complete compound in solution under specified conditions, "l" denoting a left or (-) rotation.

"Mandelonitrile," one of the molecules forming the amygdalin compound, is composed of benzaldehyde and cyanide. The mandelonitrile as a separate compound is dextrorotatory or d-Mandelonitrile.[83]

The "Beta" denotes one of two possible links between mandelonitrile and the diglucoside, the other being designated "Alpha."

The "diglucoside" is a compound molecule making up amygdalin. The diglucoside in this molecule consists of two d-glucose units having a beta linkage, known as gentiobiose.

The optical rotation of the d-gentiobiose portion as a separate compound undergoes mutorotation in aqueas solution but is stable within the amygdalin compound.[86]

The optical activity of a compound which is either dextrorotatary (d), rotating a light beam to the right, or levorotatary (l), bending the light beam to the left, is determined by optically active carbon centers in the compound. Carbons having four single bonds, with each bond holding a different atomic structure, become optically active centers. In the case of amygdalin, there are 11 active centers, five in each sugar and one at the junction connecting the phenyl group to the "CN" group in the

mandelonitrile portion or, one in the mandelonitrile grouping in the molecule.

The active centers in the gentiobiose are stable under normal environmental and manufacturing processes typical of sugars. However, the asymetric optically active center at the CN group will undergo racemic modification (with reference to this single carbon) under conditions such as described below and an epimeric modification of the amygdalin compound results.[80]

The specific sense of optical rotatation caused by an asymetric carbon center depends on the orientation of the groups held by the carbon. In space there are only two possible configurations which result in the dextro or levo optical rotation. If all the active centers change from one state, to another, the compounds are mirror images and are referred to as enantiomers.

These enantiomers will then be either dextro or levo rotatory and an equal mixture of the enantiomers is called a racemate, where 50% of the enantiomers are dextrorotary and 50% are levorotary, the compound then, is said to be,

optically inactive and an example would be dl-lactic acid or $\pm$ lactic acid.

In the case of amygdalin, only the asymetric carbon at the CN group shifts isomerically so that enantiomers of amygdalin do not occur. This type of modification is referred to as eperimerization (some, but not all, active centers shift), so that the term "racemic amygdalin" or racemized amygdalin is not appropriate. The term eperimeric amygdalin would be correct.

When epimerization occurs in solution with amygdalin, the normally occurring isomer, usually -37^{o}, rotates to a nominal -59^{o} at which point an equilibrium state is reached. Therefore, the common term "dextro amygdalin" is not appropriate inasmuch as all eperimeric configurations are levorotary. The indicated optical activity can be modified by the hydrolysis of mandelonitrile by the action of alkali to mandelic acid.[79] However, this is no longer amygdalin and does not occur with the extraction procedures which have been in common use.

The optical activity of the three components comprising amygdalin (two glucose residues and mandelonitrile) are all dextrorotatory, however, when the individual units, d-mandelonitrile along with two d-glucose residues are combined to form the intact molecule, amygdalin, the optical activity is levorotatory. The physical mechanism involved in the molecular interactions is obscure and is not theoretically predictable by noted authorities in the field so that the value of optical activity must be obtained emperically.

Mechanism of Reaction

The carbon in the epimeric center is bound to two electron-withdrawing groups, the phenyl group (benzene ring) and the nitrile group (CN), leaving that carbon with a partial positive charge. This penomena is referred to as the "inductive effect." The result is that the proton also bound to this center, having a positive charge, tends to be repelled or is more loosely bound to the carbon. In a basic medium containing hydroxyl groups (OH^{-}) the proton (H^{+}) is pulled off and combines with OH^{-} forming water

($OH^- + H^+$). When the proton leaves the asymetric carbon, a "site" is formed which permits any of the three remaining groups to interchange with it and move into the position vacated by the proton. Whichever group moves, that position vacated by the group becomes a "site" which in turn recovers the proton from the dissociated water to regenerate the hydroxyl ion (OH^-).

The amygdalin molecule is in a state of equilibrium between the two eperimeric forms and is in a constant state of change as long as the molecule is in a basic medium. It requires only a trace amount of base (OH^-) to initiate epimerization[80] and, in the absence of optically active impurities, accounts for the variations reported in the literature for optical activity (Value reported in the 9th Edition of the Merck Index - 42^o).

The epimerization of amygdalin results in different solubilities due to the hydroxy (-OH) group exposure as the various other groups within the molecule shift in relation to each other. The solubility of a given epimeric configuration could therefore either increase or decrease

depending upon the form. In the case of amygdalin the epimerization increases the solubility in water from a nominal .125 mg/ml to .350 mg/ml. Increased solubility in water for injectables can be achieved, however, by appropriate processing in aqueous solution or by lyophilization.

ENZYMIC ACTIVITY VERSUS STEREOCHEMISTRY

The enzymic sequential cleavage of the diglucoside from mandelonitrile is independent of epimerization. The receptor site of the enzyme beta-glucosidase, recognizes first the terminal D-glucose and second, the adjacent D-glucose, independent of the asymetric carbon center orientation in the mandelonitrile grouping. Furthermore, the decomposition of mandelonitrile to benzaldyde and hydrogen cyanide is alkaline hydrolized in vitro, rather than ezymatic, and eperimerization would not affect this decomposition.[2,79] Alkaline hydrolization is noted when cyanohydrens, including mandelonitrile, are placed in blood

plasma with the resultant detection of cyanide in a very short period of time.[81]

As previously described, amygdalin, even in a solution having a trace amount of base will undergo eperimerization.[80] Amygdalin, injected, therefore will undergo eperimeric modification because the blood is slightly basic and heavily buffered with a normal pH of 7.4.[55] Likewise, oral amygdalin, when it reaches the alkaline medium of the intestines, would also undergo epimeric modification.

Claims alleging that levorototary amygdalin is the only effective compound and that the dextro material is ineffective are misleading since as previously discussed, there is no such compound as dextro amygdalin, all epermic forms being levorotatory.

Confusion over the effects of stereochemistry of amygdalin arises from the failure to distinguish the mechanisms of plant reactions from those of animal or man, and from standard stereo notations in some early works.[79]

Enzymatic hydrolysis of amygdalin by emulsin in almonds was first reported by Woler and Liebig (1837).

Haisman and Knight (1967) concluded that emulsion contained three enzymes, two Beta-glusidases which converts amygdalin to prunsin then to mandelonitrile. The third enzyme catalyzes the dessociation of mandelonitrile of mandelonitrile to benzaldehyde and HCN,[83] this enzyme oxynitrilase or hydroxynitrile lyase leads to specificity of mandelonitrile, but this is a plant enzyme and is not available in man.[84,85] The alkaline hydrolysis of mandelonitrile in animal or man eliminates the stereo specific requirement for decomposition.

Furthermore, as previously mentioned, epermerization will occur in blood plasma and the asymetric carbon at the nitrile group will be in a constant state of change from one isomer to another, so that any epermeric modification produced commercially is therapeutically inconsequential.

It should be pointed out however, that the rotation of amygdalin is a result of manufacturing processes in common use and any alteration of the manufacturing process in common use would introduce an unknown variable

and would be in contrast to the good manufacturing practices code of the Federal Food and Drug Administration.

It should also be noted that earlier works referred to dextro and levo amygdalin, but it has been pointed out that the term dextro or -d- is inappropriate.[79] The notations dextro and levo referred to the mandelic group only rather than to the entire molecule. In present terminology, the prefixes "d" and "l" refer to the behavior of the entire molecule in the polarimeter.

There is nothing in the literature, theory or practice to substantiate that epemerization of amygdalin affects its therapeutic efficacy which is in good agreement with the empirical evidence in the amygdalin factories and clinics over the past years. The amygdalin in common use has been a partially epermized aqueous solution of approximately three grams in 10 ml of water and derived from non-buffered alcohol extractions. The nominal rotation of this aqueous solution is $-45^{o}(a)\ \frac{20}{D} = -45^{o}$, c = 0.30.

The amygdalin used for pharmaceutical preparations (powder) conforms to the standard identification specification IS-630-RO[82] as submitted to the federal court. The optical rotation of -37.6^{o} to -42^{o} is common with the extraction procedures which have been in common use.

CYANIDE CLEAVAGE FROM MANDELONITRILE UNDER BASE CONDITIONS

Mandelonitrile consists of a phenl group (benzene ring) connected to an asymetric carbon which in turn is connected to a hydroxy group (OH), a nitrile group (CN) and a hydrogen (H).

The hydrogens on both the hydroxy group and the asymetric carbon are "active," and are able to dissociate under basic conditions, or in a hydroxyl (OH^{-}) environment.[55,80] The basic cleavage mechanism involves the proton H^{+} in the OH group binding to a solvent hydroxyl group, OH^{-}, leaving an electron on the oxygen.

The oxygen, following the removal of the proton, then forms a double bond with the asymetric carbon (which

would result in a fifth bond to the carbon), which then results in the release of the nitrile group (CN) as CN^-.

When the nitrile group leaves the asymetric carbon, it also takes with it one electron yielding CN^-, and the electron left in the oxygen when the proton (H^+) dissociated fills the vacancy in the asymetrical carbon yielding a carbon-oxygen double bond.

The liberated CN^- then interacts with the dissociated water ($OH^- + H^+$) and combines with the proton H^+, generating HCN or hydrogen cyanide.

The CN cleavage from the asymetric carbon in the presence of the hydroxyl ion (OH^-) occurs with free mandelonitrile, but is stable with either amygdalin or Laetrile, because the proton (H) in the OH group is replaced by a bond to carbon in the adjacent glycon (glucose or glucoronic acid).

BETA-GLUCOSIDASE

The availability of beta-glucosidase is an important consideration in amygdalin therapy. One of the primary

sources of beta-glucosidase is the gastrointestinal flora. It is well known that the diet influences the balance of these gastrointestinal microorganisms and their beta-glucosidase activity.[65] Beta-glucosidase is produced in large amounts by the microorganisms Enterococci found in the lower section of the small intestine, large intestine and rectum, with its peak concentration in the large intestine.[55] Large amounts of beta-glucuronidase are also produced in the intestinal flora by Escherichia coli.[55]

Studies have shown that populations which have largely vegetarian diets with little fat or animal matter have a lower incidence of colon cancer and higher beta-glucuronidase activity than do populations which ingest large amounts of fat and animal protein.[65]

Beta-glucosidase is found in soluble form in the liver and intestines and does not exhibit latency.[66] Beta-glucosidase is found in insignificant or trace amounts in the blood in the order of .00016 micromoles per liter.[67]

Beta-glucosidase is membrane-bound in lysosomes on the inside of the bilipid membrane and does not "leak" out

of the lysosome. Therefore, it is not typically available in any appreciable concentration in the plasma or matrix of the cancer or hostal cells.[54] For this reason little or no direct hydrolysis is manifested with intratumoral injections of amygdalin.

Fasting markedly increases the activity of both beta-glucosidase and beta-glucuronidase.[69] Humans with Goucher's Disease are deficient in beta-glucosidase, and this enzyme must be supplemented for these patients. Beta-glucosidase as mentioned above has been found in the membranes of red blood cells but whether this contributes to any significant hydrolysis is obscure.[78]

The inhibition of beta-glucosidase by dietary factors needs additional research but it is known that beta-glucosidase from intestinal microorganisms is inhibited by 1:4 and 1:5 lactones of gluconic acid.[70]

The cleavage of the two D-glucose molecules from amygdalin to yield mandelonitrile is dependent on beta-glucosidase activity, which in turn is related to diet. (Enteroccoci)

Beta-glucosidase activity is one limiting parameter in amygdalin-based metabolic therapy. The amygdalin which has not been hydrolyzed or metabolized will be excreted intact in the urine. The estimated half-life of amygdalin in plasma is from 3 to 6 hours.

RECTAL OR ENEMA ADMINISTRATION OF AMYGDALIN

As pointed out previously, the specific hydrolizing enzyme Beta-glucosidase reaches its peak concentration in the lower intestine, which results in the cleavage of the two glucose molecules from amygdalin. In addition the pH of the lower intestine is alkaline which will hydrolyze the mandelonitrile to benzaldyde and hydrogen cyanide.

Enema administration therefore is the most toxic route and should be used with extreme care for the above reasons. Serious side reactions have resulted from less than one gram rectally[87] and at least one death may be attributed to enema administration.

BETA-GLUCOSIDASE, GLUCOSE AND AMYGDALIN

Beta-glucosidase, glucose and amygdalin enhance tumor hyperacidulation through intravenous infusions. The glucose lowers the pH of the cancer cell from a normal 7.3 to 5.7, enhancing glucuronide breakdown, and the beta-glucosidase supplementation enhances the hydrolization of the two glucoses from the amygdalin compound, which is the first step in the biosynthesis of Laetrile. In vivo studies show significant tumor regression in carcinosarcomas in 5 to 20 gram tumors.[64]

Before discussing further the biochemical pathway it is necessary to review the detoxification process which occurs in the liver and, to a lesser extent, the kidneys.

THE FORMATION OF GLUCURONIDES AS A DETOXIFICATION PROCESS

One of the body's primary mechanisms for the removal of certain toxic substances is to couple them with glucuronic acid, hence forming a glucuronide. The glucu-

ronide is ionic because of the free carboxyl group (CO_2H) and as such is much less able to penetrate a lipid membrane than was the original toxic substance. Glucuronides tend therefore to be biologically inert and are readily eliminated in the urine.[36] It is this glucuronide metabolic pathway which is responsible for the formation of D-l-mandelonitrile glucuronide or laetrile.

In the liver the toxic substance (alcohol or amine), specifically mandelonitrile, is coupled to glucuronic acid by employing the co-factor uridinediphosphoglucuronic acid (UDPGA), through the action of the enzyme, urdine diphosphoglucuronyltransferase (UDPG transferase), with the concurrent formation of uridine diphosphate (UDP). The result is the glucuronide of the toxic substance.[3,4]

The membrane-bound enzyme, UDPG transferase, is unusual in that its active site is masked by lipids.[56] Unless the toxic substance has some degree of solubility in the particular lipids covering the enzyme, the substrate will not contact the active site and glucuronide formation will

not occur regardless of the presence of the co-factor UDPGA.[5]

UDPG transferase is dormant until about the time of birth. One of the functions of this enzyme is to produce the glucuronide of toxic billirubin, which accounts for the concern at the time of birth over whether this activity is actually underway.[7] The enzyme may become dormant again at any time in adults and in extreme cases results in Gilbert's syndrome, in which there is an almost complete cessation of glucuronide formation.[8]

ASPIRIN TEST

A simple clinical test may be made to indicate the degree of activity of UDPG transferase. A gram of aspirin is adminitered orally and after 24 hours the urine is examined for the presence of the glucuronide of salycylic acid. It has been found that there are wide variations among adults in the ability to form glucuronides.[8] Research is currently underway aimed at developing a simple assay for detection of specific glucuronides.

MYRISTIC ACID

It has been shown that the lipid acceptor[9] for the toxic substance in the glucuronidation process exhibits maximum activity when myristic acid is available in the diet.[10] Myristic acid is a 14-carbon saturated fatty acid which apparently is incorporated into the lipid material, hence increasing the activity of UDPG transferase.[11,12] This reality, together with many other necessary dietary factors outlined below, may account in part for the variable activity of this enzyme in adults[10] and the resultant ability to form glucuronide conjugates.

OTHER UDPG TRANSFERASE DIETARY FACTORS

Other factors which influence the activity of UDPG transferase are:

1. The enzyme is stimulated by a low-protein diet.[13]
2. Moderate amounts of alcohol stimulate its activity while excessive amounts depress it.[14]

3. Lecithin acts as a stimulant.[6]
4. RNA acts indirectly as a stimulant.[15]
5. Vitamin E acts as a stimulant.[16]
6. Manganese stimulates it indirectly by stabilizing the precursors of the co-factor UDPGA.[17] (Foods containing large amounts of managnese are: certain spices: (cardamom, ginger, cinnamon, clove), the brans: (rice, wheat, buckwheat), certain herbs: (sorrel, dock, dandelion leaf), tea leaves and orange marmelade.[18]
7. The commonly used food preservative BHA almost completely inhibits the enzyme while BHT is without effect.[19]
8. UDPGA may be administered in supplemental amounts.[21]
9. Uridine monophosphate (UMP) may also be supplemented.[22]
10. Excessive use of aspirin should be avoided.[24]
11. Excessive use of chlorpromazine should be avoided.[25]

12. The divalent ions of calcium and magnesium act as stimulants.[26,27]
13. Selenium acts indirectly by preventing lipid membrane modifications.[73,75]

GLUCURONIC ACID

Glucuronic acid, which is an integral part of the production of glucuronides, is derived from glucose metabolism and is formed by the oxidation of iridine diphosphoglucose in a two-step process. This may shed some light on the fact that individuals with sugar dysfunction problems have a statistically significant higher rate of cancer.

SELENIUM

Selenium is a component of the enzyme glutathione peroxidase, which breaks down hydrogen peroxide. Hydrogen peroxide breaks down unsaturated fatty acids in bilipid membranes. It may be postulated that increased glucuronidation with selenium supplementation is due to the inhibi-

tion of hydrogen peroxide modification of the lipids surrounding UDPG transferase.[73,75]

INSULIN

An adequate supply of insulin is essential to maintain fully the capacity of the liver to form glucuronic acid conjugates, or glucuronides. Insulin acts by increasing liver uridine diphosphoglucose (UDP) dehydrogenase activity and thus supplies additional UDPGA for conjugation.[37]

Those who are suspected of having high levels of blood sugar should also undergo testing. Insulin deficiency has been shown to be associated with low levels of UDPGA, as much as a 50% decrease. Those having inadequate insulin levels should be supplemented.[37]

BIOCHEMICAL PATHWAYS (Continued)

We now return to the biochemical pathway of amygdalin with the realization that mandelonitirle, in fact a secondary alcohol, resulting from the stepwise removal of gentiobiose through beta-glucosidase activity is recognized

as a toxic substance by the detoxification process. In individuals with an adequate detoxification system this results in the synthesis of D-l-mandelonitrile glucuronide, commonly known as laetrile.

Hence, we may say that laetrile is produced primarily in the liver by the detoxification process during amygdalin therapy provided the detoxification system is adequate.

Considering the above-described biochemical chain of events, it is now apparent why it is of the utmost importance for the patient undergoing amygdalin therapy to have a detoxification system which is adequately synthesizing laetrile from the breakdown product of amygdalin.

LEAKY MEMBRANE

Malignant cells possess what has been termed a "leaky membrane," referring to the outer or plasma membrane of the cell.[20] Small organic molecules readily diffuse across this membrane in a manner not characteristic of normal cells. A second significant difference between malignant and normal cells is the leaky membrane surround-

ing the small cytoplasmic sacs known as lysosomes, which contain a variety of hydrolyzing enzymes. It is known that in malignant cells the lysosomal contents leak into the cytoplasm and thereby make available for cellular activity — among others — the enzyme beta-glucuronidase.[23,28,29]

MITOCHONDRIA

The mitochondria are subcellular organelles and are the so-called "energy factories" of the cells which receive stored oxygen from myoglobin. Myoglobin consists of a single polypeptide chain and one "heme" group. Myoglobin combines with oxygen released by the red blood cells and transports it to the mitochondria, where the oxygen degenerates into biochemical energy by the combustion of glucose to carbon dioxide and water thereby generating stored energy in the form of ATP (adenosine triphosphate) in the process called "oxidative phosphorylation."

Just how the breakdown of glucose transfers energy to ATP is obscure and controversial. In England, Peter

Mitchell received a Nobel Prize in October, 1978, for his theory of "chemiosmotic coupling," based on a "proton gradient" as a physical mechanism. his theory suggests that protons are transported across the mitochondrion membrane, creating an ion gradient whose potential energy is transferred to ATP.[76]

The transmembrane pH difference (pH of mitochondrion matrix vs. pH of cytoplasm) governs the ionic substrate translocation across the mitochondrial membrane[35] and the swelling of the membrane. The increase in alkalinity is accompanied by mitochondrial swelling resulting in a considerable loss of co-factors and an uncoupling of oxidative phosphorylation. Not only does diet play a role in the shape and function of the mitochondria, but psychological or nervous factors also have a physiological effect on this condition which may account in part for the effects of positive mental attitude. Very little is known about the mechanism controlling these morphological changes within the cell, but they do directly inhibit the exchange-diffusion reactions across the mitochondrial

membrane which in turn have an effect on aerobic and anaerobic balance.[34]

Cytochrome oxidase normally binds molecular oxygen in the same manner as the "heme" group in hemoglobin. The cyanide ion has the ability to displace oxygen from this site, which inhibits enzyme activity.[31,32] If this blockage continues for a sufficient length of time, cell death will result. Moreover, the cytoplasm of malignant cells is more acidic than that of normal cells due to the increased production of lactic acid.[33] In contrast, the mitochondria are somewhat alkaline.[34] The significance of these pH differences is that mandelonitrile will have a tendency to remain intact and not break down in an acid medium of the cytoplasm but will split in the alkaline medium inside the mitochondrion with the resultant release of cyanide and banzaldehyde in the mitochondria. (See previous discussion — Cyanide Cleavage from Mandelonitrile Under Base Conditions.)

An additional influence of diet on amygdalin therapy is that the mitochondria becomes more alkaline and the

cytoplasm becomes more acid during fasting periods or low-protein ingestion.[34]

LYSOSOMES — VITAMIN A

The enzyme beta-glucuronidase, which leaks from the lysosomes of cancerous cells, has a pH optimum of 5.2. It is known that glucose administration selectively lowers the pH of tumor cells thereby increasing the effectiveness of this enzyme.[36] Administration of 500,000 units or more of Vitamin A results in an increased leakage of beta-glucuronidase from lysosomes as well as a significant increase in the blood glucose level.[57] The result of megadoses of Vitamin A administration is therefore twofold — it not only causes the liberation in greater quantities of beta-glucuronidase from lysosomes but also indirectly lowers the pH of the cancer cell, thereby increasing the activity of this enzyme.

D-GLUCARIC ACID

One of the known effective inhibitors of beta-glucuronidase is D-glucaric acid (D-glucosaccharic acid).[58] This acid is normally produced in the liver in small amounts and excreted in the urine. Studies have shown that the amounts produced vary from one individual to another.[59] It has been demonstrated that the administration of phenobarbital and other barbiturates possibly used in cancer therapy greatly increases urinary levels of this metabolite. Other drugs (e.g., progesterone, diphenylhydantoin) also cause a greater production of this powerful inhibitor of beta-glucuronidase[60] and some individuals produce much more of D-glucaric acid than do others.[59] Considerable research is underway concerning this substance and assays have been developed for glucaric acid determination. The presence of this strong inhibitor, which research has shown will penetrate cell membranes,[60] could be a limiting factor in the hydrolysis of laetrile at the malignant lesion, and it is suspected that increased levels of this inhibitor may

account for the wide variation of beta-glucuronidase activity within a given species.[58]

The following drugs stimulate the production of glucaric acid as measured in the urine and should be avoided:[60,61,62]

1. Phenobarbital and other barbiturates
2. Progesterone
3. Diphenylhydantoin (used in the treatment of epilepsy)
4. Contraceptive pills including but not limited to: Ovulen, Orthonovin, Gynovlar, Conoved E

In addition to glucaric acid, which is also found in the pectin-gel of sunflower seeds, the naturally occurring isomer, laevorotatory malic acid found in apples is an effective inhibitor of beta-glucuronidase.[58]

The variation between patients in the concentration of glucaric acid may be a significant factor in amygdalin-based metabolic therapy.

BETA-GLUCURONIDASE

The enzyme Beta-glucuronidase is capable of splitting the glucuronide, D-l-mandelonitrile-beta-glucuronide, or laetrile, into its components. One of them, mandelonitrile, then spontaneously breaks down under slightly alkaline conditions to benzaldehyde and hydrogen cyanide. As far as is known, this is not an enzyme reaction but is pH dependent in man.[30]

The specificity of toxic cyanide from laetrile for malignant cells lies in the leakage of beta-glucuronidase from the lysosomes of these cells into the cytoplasm as compared to leakage of this enzyme in normal cells.[28] Too, it is known that glucuronides do not enter normal cells and are biologically inert.[36]

Beta-glucuronidase is one of the lysosomal enzymes with a pH optimum of 5.2 and is widely distributed throughout the body with a considerable variation in activity within a given species.

Malignant cells have a considerable increase in beta-glucuronidase activity due to the leaky lysosomal membrane

and the enzyme is present in the serum due to the leakage through plasma-cell membranes.[28]

Increase in beta-glucuronidase leakage from lysosomes can be increased by a factor of 400 measured in blood serum with the injection of 500,000 units of Vitamin "A." In addition, Vitamin A can cause an increase in blood sugar levels in excess of 135 mg%.[57]

Above 10,000 units Vitamin "A" must be taken in the emulsified form in order to avoid toxicity to the liver. Micronic, emulsified, fat soluble vitamins are absorbed by the villi into the lymph ducts and are transported to the systemic circulation, thus bypassing the liver. Highly concentrated emulsified Vitamin A has been given in amounts in excess of a million units daily without liver retention or reported side effects. Some side effects, however, may be encountered, but they are completely reversible.

An integral part of the holistic metabolic therapy is the plasma membrane transport system in the malignant

cell. Enzymes, vitamins, minerals and hormones all play a role in these systems.

From what has been presented it appears that the variable response noted in the treatment of malignancy with amygdalin may result in part from individual differences in the patient's ability to synthesize glucuronides, as well as in the activity of the specific hydrolyzing enzyme, beta-glucuronidase. If this is true the widespread application of a simple clinical test for glucuronide formation and beta-glucuronidase activity in relation to amygdalin response would lead to a statistically significant correlation between these variables.

Those individuals showing a deficiency in glucuronide synthesis or glucuronidase activity would undergo a treatment of metabolic and dietary supplements until normal levels are restored. Amygdalin therapy response will increase when it can be demonstrated that the patient possesses a detoxification system capable of sufficient glucuronide synthesis and with sufficient beta-glucuronidase activity at the malignant site.

EDTA AND TRYPSIN

It has been shown that cancer cells have a reduced calcium level in the cell bilipid membrane and fewer glycoproteins. EDTA assists in removing a portion of the glycoprotein cell coat of cancer cells by chelation of Ca^{++} bridges. In contrast, trypsin produces a deeper enzymatic cleavage that affects the structural integrity of the bilayer lipid cell membrane.[51]

This is corroboration of the empirical evidence of practicing physicians that moderate EDTA chelation therapy improves the patient's response to laetrile-based metabolic therapy. For a more detailed dissertation on chelation therapy, see Protocols for Chelation Therapy, American Academy of Medical Preventics (AAMP).

DMF

DMF (N,N-Dimethylformamide) has been shown to induce morphological differentiation and reduction of

tumorigenicity in cultured mouse cells (rhabdomyosarcoma cells), as well as in vivo studies with mice.

Properties of cells became more like normal cells rather than malignant cells.[72]

GERMANIUM

Organogermaniumsesquioxide it is speculated affects tumor dimunition because of the ability of the compound to loosely bind oxygen which in turn is carried to the cancer cell, affecting the anaerobic energy process. This compound also has been used as an effective hypertensive agent.[68,71]

THIOSULFATE - THIOCYANATE

Thiosulfate acts by penetrating the mitochondrial membrane where it furnishes sulfur to rhodanese in the presence of cyanide to produce thiocyanate.

Thiocyanate is a natural hypotensive agent and can be supplemented for the treatment of hypertension at blood serum levels from 8 to 30 mg percent.[75] The normal

thiocyanate level is proportional to the amount of nitrilosidic food — that is, foods containing cyanogenic compounds — in the diet. Those who are accustomed to typical Western eating habits have thiocyanate levels 5 to 8 times lower than those of cultures in which much higher levels of nitrilosides are ingested, a fact which forms the basis for the theory that adequate nitriloside (also designated Vitamin B17) may be the preventive factor, or at least a major factor, in the prevention of cancer and very likely of other conditions.

Thiocyanate is found in maximum concentration in the thyroid where it affects the production of thyroxin, a natural blood pressure regulator.[77] Iodine supplementation may be used to normalize thyroxin in the presence of elevated thiocyanate levels.

It is commonplace to observe a lowering of high blood pressure in patients undergoing amygdalin-based metabolic therapy.

Thiocyanate also is an effective inhibitor of ATPase, an enzyme necessary in the conversion of ATP to ADP in the aerobic glycolysis pathway of cells.[45]

RHODANESE

It has been stated that one of the decomposition products of mandelonitrile is hydrogen cyanide or its active form, the cyanide ion (CN^-). The detoxification of cyanide is brought about by the enzyme rhodanese, which utilizes thiosulfate to convert toxic cyanide to nontoxic thiocyanate.[38] Rhodanese is found only in the mitochondrion,[39] the principal site of mandelonitrile decomposition. The uptake of anions, including Laetrile, by mitochondria is discussed more fully below.

HCG

Human chorionic gonadotropin (HCG) is found in cancer cells[63] and during pregnancy. HCG is a powerful inhibitor of rhodanese[40] which allows cyanide liberated from mandelonitrile decomposition to survive conversion

to nontoxic thiocyanate. Thus, cyanide is free to inhibit both the iron-containing enzymes of the respiratory pathway including cytochrome oxidase, as well as inhibit aldehyde oxidase allowing benzaldehyde to effect the glycolysic pathway and pyruvate dehydrogenase effecting the oxidative pathway (to be discussed later).[31,32]

GLYCOLYSIS

The biochemical pathway from glycogen to lactic acid is known as glycolysis. Under aerobic conditions the immediate precursor of lactate (pyruvate) is further metabolized by the tricarboxylic acid cycle thus preventing an accumulation of lactic acid (Pasteur effect). Under anaerobic conditions (fermentation) the metabolism of pyruvate does not occur due to a biochemical defect in the tricarboxylic acid cycle. Because of the oxygen deficiency lactate accumulates resulting in a lowering of cellular pH (Warburg effect).[33,42]

It is postulated that in cancerous cells the fermentation pathway is converting pyruvate to lactate resulting

from an impaired tricarboxylic acid cycle. This defect drops cellular pH values to as low as 5.7 causing a pH gradient across mitochondrial membranes.[33] The typical mitochondrial pH value of 7.4 may assist in the uptake of mandelonitrile by mitochondria. Mandelonitrile glucuronide (that is laetrile) being an anion (negatively charged) should be incorporated into the mitochondria of cancerous cells at a greater rate than into those of normal cells.[35]

PYRUVATE KINASE

It has been pointed out that there are in the cancerous cell two biochemical pathways related to the utilization of sugar — namely, the respiratory (aerobic) pathway and the so-called alternate pathway or fermentation (anaerobic) one, which results in the production of lactic acid.

Pyruvate kinase is an enzyme which is a determinant in the proportion or balance between these two pathways. An inhibition of pyruvate kinase stimulates the respiratory rate and concurrently decreases the glycolytic rate of the cell. A realization of this effect may be put to practical

use when considering that one of the known inhibitors of pyruvate kinase is the essential amino acid phenylalanine.[42] Incorporation of large amounts of phenylalanine into the diet may swing the balance between the respiration and fermentation pathways away from the fermentation mode.

Certain foods contain larger amounts of this essential amino acid than others — including, in decreasing order, casen (milk protein), wheat gluten, low fat soybean meal and dried brewer's yeast.[43]

BENZALDEHYDE

The presence of the two biochemical pathways of sugar metabolism in cancer cells indicates that the effectiveness of cell damage through cyanide alone is limited. The alternate pathway provides a means whereby the cell may continue to survive even though respiration is inhibited by cyanide.[41] The second of the two decomposition products of mandelonitrile — namely, benzaldehyde — acts to inhibit the alternate pathway, as will be discussed. Thus, each of the two products resulting from

the breakdown of amygdalin acts predominantly on one of the two biochemical pathways necessary for cell survival.

Research has shown that there is a toxic, synergistic effect between cyanide and benzaldehyde.[44]

A critical step in glycolysis is the conversion of ATP to ADP by mitochondrial ATPases.[45] Oxidation cannot proceed without ADP thus linking the two pathways (aerobic and anaerobic) together. Benzaldehyde has been shown to inhibit both the sodium, potassium and magnesium ATPases.[43] The amino acid cysteine protects ATPase from inhibition by aldehydes, including benzaldehyde.[46] Since cysteine is one of the sulfur-containing amino acids this result implies that excessive sulfur in the diet may impair the inhibition of ATPase by benzaldehyde.

THIOCYANATE VERSUS ATPase

It has also been shown that the thiocyanate ion resulting from detoxification of cyanide also inhibits ATPase.[47]

ANALGESIC EFFECT

It has long been known that benzaldehyde has an analgesic effect in the treatment of cancer patients. This effect is caused by changes in the permeability of nerve membranes to sodium and potassium. There is an increase in membrane conduction to potassium and a concurrent decrease in permeability to sodium relative to potassium, which in turn inhibits the firing of the neuron.[48]

Both benzaldehyde and its metabolite, benzoic acid, increase nerve membrane conduction to potassium (K^+) and decrease the permeability to sodium Na^+ relative to potassium, inhibiting nerve activity.

ALDEHYDE OXIDASE

Human liver aldehyde oxidase has the ability to oxidize aldehydes (including benzaldehyde) to the corresponding carboxylic acids thus reducing the effectiveness of benzaldehyde inhibition of ATPase. However, it has been shown that cyanide is an inhibitor of aldehyde oxidase,

thus preserving to some degree the effectiveness of benzaldehyde as an analgesic and its inhibition of ATPase.[49]

PYRUVATE DEHYDROGENASE

The conversion of pyruvate to a form required for entering the tricarboxylic acid cycle involves the pyruvate dehydrogenase complex, a set of closely related enzymes. This part of the oxidative pathway is also inhibited by benzaldehyde.[50]

WHY AMYGDALIN THERAPY MAY FAIL

Variation in cancer therapy with amygdalin results from several basic causes:

1. The cleavage of the two glucose units from amygdalin to yield mandelonitrile is dependent on beta-glucosidase activity — which, as we have seen, is related to specific inhibitors and the intestinal flora which in turn is related to diet.
2. An impaired detoxification system results in lowered synthesis of mandelonitrile glucuronide (laetrile) from

amygdalin by the body. In cancer of the liver this system may be extremely deficient because the major detoxification processes reside in this organ. As pointed out before, efficient operation of the detoxification system is certainly diet-related from many standpoints. Among these are the presence of appropriate minerals (Ca, Mg, Mn) and the absence of heavy metals which may inhibit enzyme activity (Pb, Ba, Hg).

3. The plasma membrane (or outer membrane) of cancerous cells is covered with a glycoprotein coat which may in some tumors impair the uptake of glucuronide. Remember that an integral part of metabolic therapy involves the active transport systems into malignant cells, and that the entire dietary universe — enzymes, vitamins, minerals, hormones — all play roles in this.
4. Glucuronides are normally excreted in the urine, thereby limiting the time of effective incorporation into tumor cells. Loss of laetrile through this route has been controlled through the use of drugs causing

temporary blockage of kidney function. An estimate of the half-life of laetrile in the blood is from three to six hours.[84]

5. The condition of the intestinal flora affects the production of large amounts of beta-glucosidase and beta-glucuronidase.
6. Inhibitors of beta-glucosidase and beta-glucuronidase may play an important role in amygdalin based metabolic therapy.
7. Psychological effects also play an important role in the holistic metabolic treatment program.

TREATMENT CONSIDERATION

DIET AND FOOD SUPPLEMENTS:

Low fat and animal protein

Average to low sulfur (few eggs)

Peach kernel oil (probably also apricot kernel oil) —source of myristic acid

Pollen-source of myristic acid

Lecithin

UDPGA (not available in the USA)

RNA (ribonucleic acid, usually from yeast)

Supplemental Calcium, Magnesium and other minerals

S.O.D. - superoxide dismutase

Foods High in Manganese:

Bran (rice, wheat, buckwheat)

Spices (cardamom, ginger, cinnamon, cloves)

Herbs (sorrel, dock, dandelion leaf)

Orange marmalade

Foods High in Phenylalanine:

Casein (milk protein)

Wheat Gluten

Low fat soybean meal

Dried brewer's yeast

AVOID:

BHA — butylated hydroxy anisole (an antioxidant food preservative found in margarine and other foods)

Excessive Alcohol

Excessive Aspirin

Certain female contraceptives (drug type)

Certain other drugs including chlorpromazine, phenobarbital and other barbituates, diphenylhydantoin, progesterone

Excessive apples

Excessive sulfur-containing foods (eggs)

ADDITIONAL TREATMENT:

EDTA Therapy

Megavitamin dosages of emulsified vitamins A and E

Megavitamin dosages of vitamin C

Occasional fasting

Test for the patient's ability to produce glucuronides

Test for the patient's ability to hydrolize amygdalin

Test for the patient's activity of specific inhibitors of glucuronidase and glucosidase

Selenium

Germanium sesquioxide

Enzyme supplements

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GLOSSARY
(Definitions Applicable to the Usage in this Text)

Adaptagen — A non-specific immune stimulant.

Amine — An organic substance containing saturated nitrogen.

Aldehyde oxidase — An enzyme found in the liver which converts aldehyde to the corresponding carboxylic acid (benzaldehyde to benzoic acid). Inhibited by cyanide.

Amygdalin — A disaccharide derivative of mandelonitrile consisting of benzaldehyde cyanohydrin coupled to a linear chain of two D-glucose residues (gentiobiose).

ATP (adenosine triphosphate) — A phosphorylated derivative of the nucleic acid (RNA, DNA) component adenosine, containing the high energy triphosphate linkage.

ATPase — An enzyme which cleaves one phosphate group from ATP, resulting in the diphosphorylated derivative ADP.

Benzaldehyde — An oxidation product of benzyl alcohol. The simplest aromatic aldehyde (C_6H_5CHO). Oxidized to benzoic acid by aldehyde oxidase. An analgesic and specific enzyme inhibitor.

Benzoic Acid — The simplest aromatic Carboxylic acid ($C_6H_5CO_2H$). Results from oxidation of benzaldehyde by aldehyde oxidase. An analgesic.

Beta-Glucosidase — An enzyme found in most all tissues which cleaves terminal D-glucose from polysaccharides or polysaccharide derivatives including amygdalin.

Beta-Glucuronidase — An enzyme found in lysosomes which is capable of cleaving glucuronides including laetrile.

Biologicals — A European term describing adaptagens.

Cyanide — An organic grouping consisting of one carbon and one nitrogen atom, having a unit negative charge.

Cysteine — A sulfur-containing amino acid which bears the sulfhydryl group (-SH). Cysteine protects ATPase inhibition from aldehydes including benzaldehyde.

Cytochrome oxidase — An enzyme found in mitochondria related to the utilization of oxygen in the formation of water and heat. A part of the electron transport system.

Divalent ion — An ion having a charge of two (2).

Dextro isomer (+)(S) — A substance capable of rotating polarized light clockwise.

D Glucuronic Acid — Produced by a two step oxidative process from D Glucose. A monocarboxylic anion. The saccharide portion of laetrile.

DMF (dimethylformamide) — An organic solvent which is the dimethyl amid of formic acid having the formula $HC(O)N(CH_3)_2$. Recently shown to have an effect on cancer cell differentiation.

DMSO (dimethylsulfoxide) — An organic solvent which dissolves difficultly soluble substances. Capable of penetrating cellular membranes (a carrier solvent).

EDTA (Ethylenediaminetetraacetic acid) — An organic substance capable of chelating or solubilizing calcium and other divalent ions.

Ehrlich ascites tumor cells — A particular type of cancerous cell much used in research characterized by a high glycolytic rate and high contact inhibition.

Enantiomers — The specific stereoisomers that are mirror images due to racemization of all the optically active centers — not applicable to amygdalin or laetrile.

Electron transport system — A biochemical process concerned with a series of cytochromes related to the utilization of oxygen. Takes place in the mitochondria.

Epimers — Specific stereoisomers that are characterized by racemization of a part of the optically active centers, but not all the optically active centers. Amygdalin and laetrile exhibit experimerization in the presence of hydroxyl groups or bacic medium.

Estrogen — A steroid hormone that induces estrus.

Glucaric acid — A powerful inhibitor of beta-glucuronidase produced in small amounts in the liver of healthy individuals. Excessive activity will interfere with laetrile metabolism.

Glucuronides — Organic substances consisting of glucuronic acid coupled to an alcohol or an amine.

Glycolysis — The metabolic pathway from glycogen to lactic acid, representing the failure to metabolize pyruvic acid through the tricarboxylic acid cycle.

HCG (Human chorionic gonadotrophin) — A glyco-protein consisting of two peptide chains, alpha and beta, found in cancer patients and during pregnancy. Inhibits the enzyme rhodanese.

Hydrogen cyanide (HCN) — A grouping consisting of a cyanide ion plus a proton —a non-charged molecule.

Insulin — A protein hormone acting on the pancreas relating to the metabolism of sugar.

Lactate dehydrogenase — An enzyme which converts lactic acid to pyruvic acid or the reverse. An integral part of the glycolysis pathway.

Lactic acid — The metabolic product resulting from the hydrogenation of pyruvic acid.

Lactic Dehydrogenase — An enzyme which converts lactate to pyruvate and the reverse action of pyruvate to lactate (anaerobic pathway).

Laetrile — A derivative of mandelonitrile consisting of benzaldehyde cyanohydrin coupled to glucuronic acid.

Levo isomer (-)(R) — A substance capable of rotating polarized light counterclockwise.

LD_{50} (Lethal dose fifty) — The amount of a substance which is expected to kill 50% of a population of experimental animals.

Lysosome — A sub-cellular component (organelle) found in the cytoplasm consisting of a membranous sac enclosing various enzymes.

Mandelonetrile C_6H_5CH (OH) CN — Benzaldehyde cyanohydrin resulting from the hydrolysis of amygdalin and other cynogenic glycosides. A component of laetrile.

Mitochondrion — A small subcellular component which utilizes molecular oxygen in the production of ATP. Also called the "energy factory of the cell."

Myristic acid — a 14-carbon saturated fatty acid which optimally stimulates the enzyme responsible for synthesizing glucuronides (UDPG transferase).

Optical activity — The rotation of polarized light by a substance containing asymmetric carbon centers.

Optical isomers — An organic substance containing one or more asymmetric carbon centers (a carbon bearing four different groups) resulting in optical activity.

Oxidative phosphorylation — A biochemical process which applies phosphate groups to the substances of the tricarboxylic acid cycle resulting in the production of ATP.

Pasteur effect — The failure of lactic acid to accumulate in a cell due to the metabolism of its precursor pyruvic acid by the tricarboxylic acid cycle.

Phenylalanine — One of the essential amino acids. Inhibits pyruvate kinase.

Prunasin — A monosaccharide derivative of mandelonitrile consisting of benzyaldehyde cyanohydrin coupled to a D-Glucose residue.

Pyrophosphate — Two phosphate groups coupled together.

Pyruvic acid — An intermediate preceeding the tricarboxylic acid cycle and/or lactic acid formation.

Pyruvate dehydrogenase complex — Enzymes which convert pyruvate to a form acceptable to the citric acid or tricarboxylic acid cycle. Inhibited by benzaldehyde.

Pyruvate kinase — An enzyme responsible for the production of pyruvic acid thereby controlling the balance between the respiration and glycolytic pathways. Inhibited by phenylalanine.

Racemic modification — A mixture of equal parts of enantiomers which is optically neutral. The specific isomeric configuration characterized by mirror image configurations. Not applicable to amygdalin or laetrile.

Rhodanese — An enzyme found only in mitochondria capable of converting toxic cyanide ion to non-toxic thiocyanate ion.

Stereoisomer — A compound that has the same number and kind of atoms as another compound, and of similar structure, but of different arrangements of atoms in space.

TDL_{20} (Toxic Dose low) — The lowest amount of a substance which will produce a toxic response of any kind.

Thiocyanate — A negative ion formed by coupling one atom of sulfur to the cyanide ion, CN^-. Has the formula SCN^-.

Thiosulphate — A negative ion formed by replacing one oxygen atom of the sulphate ion, SO_4^{-2}, with sulfur. Has the formula $S_2O_3^{-2}$.

Thyroxine — A hormone containing iodine biosynthesized in the thyroid which regulates metabolism and blood pressure.

Tricarboxylic acid — An organic acid containing three carboxy groups (CO_2H).

Tricarboxylic Acid cycle (citric acid cycle) — A cyclic set of biochemical transformations resulting in energy formation in the form of ATP.

UDPGA (Uridine diphosphoglucuronic acid) — A cofactor required in the formation of glucuronides by transferase. Consists of uridine coupled to glucuronic acid through pyrophosphate.

UDP (Glucose — Precursor of UDPGA.

UDPG transferase — Uridine diphosphoglucuronyltransferase. An enzyme found principally in the liver which forms the glucuronies of toxic substances including alcohols and amines. Responsible for the formation of laetrile from mandelonitrile, the breakdown product of amygdalin.

UDP Uridine diphosphate) — A byproduct in the formation of glucuronide by UDPG transferase. A phosphorylated derivative of the nucleic acid component, uridine.

Warburg effect — The excessive production of lactate in cancer cells from a failure to convert pyruvate via the tricarboxylic acid cycle.